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Clinical Trial Design Considerations for Hospitalised Patients With Ulcerative Colitis Flares and Application to Study Hyperbaric Oxygen Therapy in the NIDDK HBOT-UC Consortium

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ABSTRACT

Background: Patients with ulcerative colitis (UC) who are hospitalised for acute severe flares represent a high-risk orphan population.

The Handling Editor for this article was Dr Colin Howden, and this uncommissioned review was accepted for publication after full peer-review.

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Aim: To provide guidance for clinical trial design methodology in these patients.
Methods: We created a multi-centre consortium to design and conduct a clinical trial for a novel therapeutic intervention (hyperbaric oxygen therapy) in patients with UC hospitalised for moderate–severe flares. During planning, we identified and addressed specific gaps for inclusion/exclusion criteria; disease activity measures; pragmatic trial design considerations within care pathways for hospitalised patients; standardisation of care delivery; primary and secondary outcomes; and sample size and statistical analysis approaches.
Results: The Truelove-Witt criteria should not be used in isolation. Endoscopy is critical for defining eligible populations. Patient-reported outcomes should include rectal bleeding and stool frequency, with secondary measurement of urgency and nocturnal bowel movements. Trial design needs to be tailored to care pathways, with early intervention focused on replacing and/or optimising responsiveness to steroids and later interventions focused on testing novel rescue agents or strategies. The PRECIS-2 framework offers a means of tailoring to local populations. We provide standardisation of baseline testing, venous thromboprophylaxis, steroid dosing, discharge criteria and post-discharge follow-up to avoid confounding by usual care variability. Statistical considerations are provided given the small clinical trial nature of this population.
Conclusion: We provide an outline for framework decisions made for the hyperbaric oxygen trial in patients hospitalised for UC flares. Future research should focus on the remaining gaps identified.

1 | Introduction

Nearly 50% of patients with ulcerative colitis (UC) will require hospitalisation for a flare at some point in their disease course [1, 2]. While UC hospitalisation rates have stabilised in western countries with compounding prevalence (stage 3 epidemiological transition period), newly industrialised countries (stage 2 epidemiological transition period) have observed rapidly increasing hospitalisation rates, contributing to an increased burden on global health care systems [3]. Among stage 3 countries, a rise in UC hospitalisation rates is still seen among Black or African Americans, Medicaid enrolees and those in rural centres where resources and access to care are limited [4].

Patients with UC hospitalised for disease flares are at increased risk for short- and long-term complications [1, 5–9]. High-dose intravenous corticosteroid therapy is the mainstay of medical therapy for hospitalised UC flares, but up to two-thirds of UC patients may be refractory to intravenous corticosteroids and require rescue therapy with biologics, small molecules and/or colectomy [10–14]. Emergent in-hospital colectomy is associated with a significant risk for post-operative morbidity and mortality, particularly in centres with limited expertise or volume [15–17]. Infliximab and cyclosporine have been affirmed as rescue medical therapies in corticosteroid non-responders [10, 13], but further research for novel rescue therapies has been limited [18–21].

The lack of research in this population is likely due to several factors. First, recruitment is challenging given the overall low incidence of hospitalisation and the rapidity with which these patients must be identified, screened, enrolled and randomised within the hospitalisation care pathway. Second, the urgency to treat due to the acuity of patients typically supersedes enrolment into clinical trials. Third, trials will need to be tailored to local patient preferences and care pathways given the preference- and time-sensitive nature of decisions in this population. Fourth, ethical issues preclude the use of placebo alone in patients who are at immediate risk for colectomy, given that intravenous corticosteroids have been the medical standard of care since the mid-1900s. Finally, no formal consensus exists for endpoints in clinical trials for UC patients hospitalised for acute flare. Thus, there is a critical need to both study novel interventions for hospitalised UC patients and to develop methodological considerations for clinical trial designs to guide future drug development in this high-risk, orphan population.

To address these clinical care and clinical trial methodology gaps, a National Institutes of Health (NIH)-National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)-sponsored consortium was created to design and conduct a clinical trial of a novel therapeutic approach, hyperbaric oxygen therapy, for UC patients hospitalised due to moderate–severe flares (HBOT-UC). During the planning phase, gaps in methodology for clinical trials of hospitalised UC patients were addressed, and an outline of a framework was created for other investigators. The outcome of the planning phase and pragmatic study design considerations for hospitalised UC flares are presented to foster collaboration in determining methodological advances to assess the efficacy of subsequent advanced medical therapies for this population.

2 | Methods

The investigators followed recommendations from the Institute of Medicine for small clinical trials [22], CONSORT-Outcomes 2022 Extension [23], and the Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) workflow to design a fit-for-purpose study in UC patients hospitalised for acute disease flares [24]. We summarise each domain within the PRECIS-2 framework with regards to how they influenced our final study design and how they can be considered for designing future clinical trials in hospitalised UC patients (Figures 1 and 2). As a final step for ensuring broader applicability of our work, a group of external experts not engaged in the trial design or conduct were invited to provide input on framework decisions for designing hospitalised UC trials and help ensure generalisability and comparability of clinical trials in this population going forward.

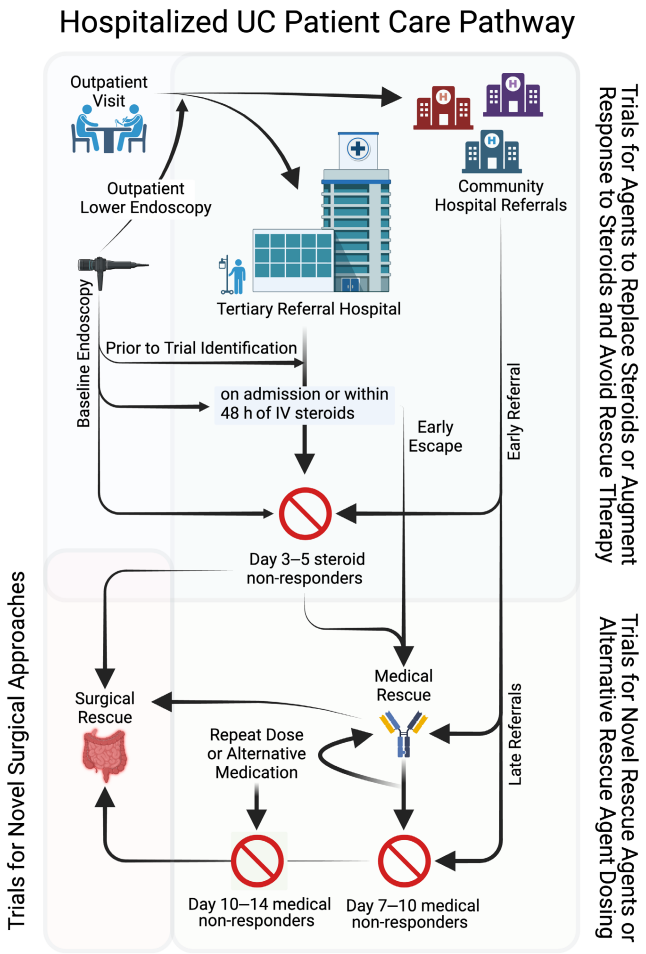

FIGURE 1 | Usual care pathway for hospitalised ulcerative colitis patients and considerations for trial designs. The usual care pathway for hospitalised UC patients was first defined to allow for determination of how different PRECIS-2 domains would need to be addressed to optimise trial design while maintaining a pragmatic approach.

3 | Eligibility: Who Is Selected to Participate in the Trial?

The goal of inclusion/exclusion criteria is to define a study population for three purposes: (1) mitigate safety concerns, (2) generate interpretable and reproducible results by creating a homogenous cohort for enrolment and (3) enrichment for outcome(s) of interest to help ensure key events are observed. This must be balanced against the broader applicability to patients seen in clinical practice that are not already well represented in traditional outpatient UC clinical trials [25]. When considering hospitalised UC patients, the consortium identified key eligibility criteria gaps needing additional attention in study design (Table 1; [26–37]).

3.1 | Severity Definition

Acute severe UC (ASUC) has been traditionally defined using the Truelove Witt's criteria indicating severe disease activity [27]: ≥ 6 blood stained stools daily, with ≥ 1 feature of systemic toxicity (haemoglobin < 10.5 mg/L, erythrocyte sedimentation rate (ESR) > 30 mm/h, fever > 37.8°C and/or tachycardia > 90 beats per min). Recent societal guidelines from the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA) and the European Crohn's and Colitis Organisation (ECCO), reaffirmed that these disease activity criteria remain the gold standard for identifying outpatients in need of hospitalisation [28–30]. Nearly one-third of hospitalised UC patients treated with intravenous corticosteroids, however, do not meet Truelove Witt's criteria, and non-response to corticosteroids was seen in up to 20% of these patients not meeting these criteria [32, 37]. Therefore, Truelove Witt's criteria do not capture all considerations for hospitalisation in real-world practice and important populations would be missed if trials of hospitalised UC patients were limited to those meeting Truelove Witt's criteria. Evidence does support the prognostic value of Truelove Witt's criteria for in-hospital outcomes, with each additional factor being associated with an incremental increase in probability for needing rescue therapy [31, 32]. However, this work is primarily limited to one geographic region, and the broader applicability was deemed uncertain. More recent work has demonstrated that alternative factors (CRP, albumin, endoscopy) are more prognostic [31, 33, 34]. Importantly, the erosion and ulceration component of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was most prognostic and moderate–severe endoscopic severity (UCEIS ≥ 4 points) was present in 96% of patients meeting Truelove Witt's criteria for ASUC, making endoscopic severity a prognostic and broadly applicable inclusion criteria for hospitalised UC clinical trials. The Mayo endoscopic sub-score (MES) is accepted by regulatory bodies, and erosions or ulcerations for UCEIS correspond to a MES of 2–3. Thus, a MES of 2–3 would also be sufficient for enrolment with secondary measurements for UCEIS.

4 | Recruitment: How Are Participants Recruited Into the Trial?

Two main time points were identified within the hospitalised UC patients care pathway for recruitment into a medical clinical trial: (1) upon admission or shortly (within 48 h) after starting intravenous steroids (prior to patients declaring themselves to be steroid responders or non-responders) and (2) after 3–5 days of intravenous steroids when patients would be identified as steroid non-responders. The objective in each group is different, with early identification focused on interventions aimed at replacing intravenous steroids and/or optimising responsiveness to steroids so patients can be discharged and have availability to receive one of the multitudes of advanced medical therapies approved for "moderate–severe disease" in the outpatient setting. The latter group will focus on testing novel rescue therapy agents or dosing strategies for existing rescue therapies to minimise disease impacts and avoid disease-related complications (colectomy, re-hospitalisation) (Figure 1 and Table 1; [38–41]).

4.1 | Disease Activity Assessment

A review of practice patterns among participating centres defined several possible scenarios for how endoscopic disease activity is currently measured for hospitalised UC flares and how this might influence recruitment feasibility (Figure 1). Broadly,

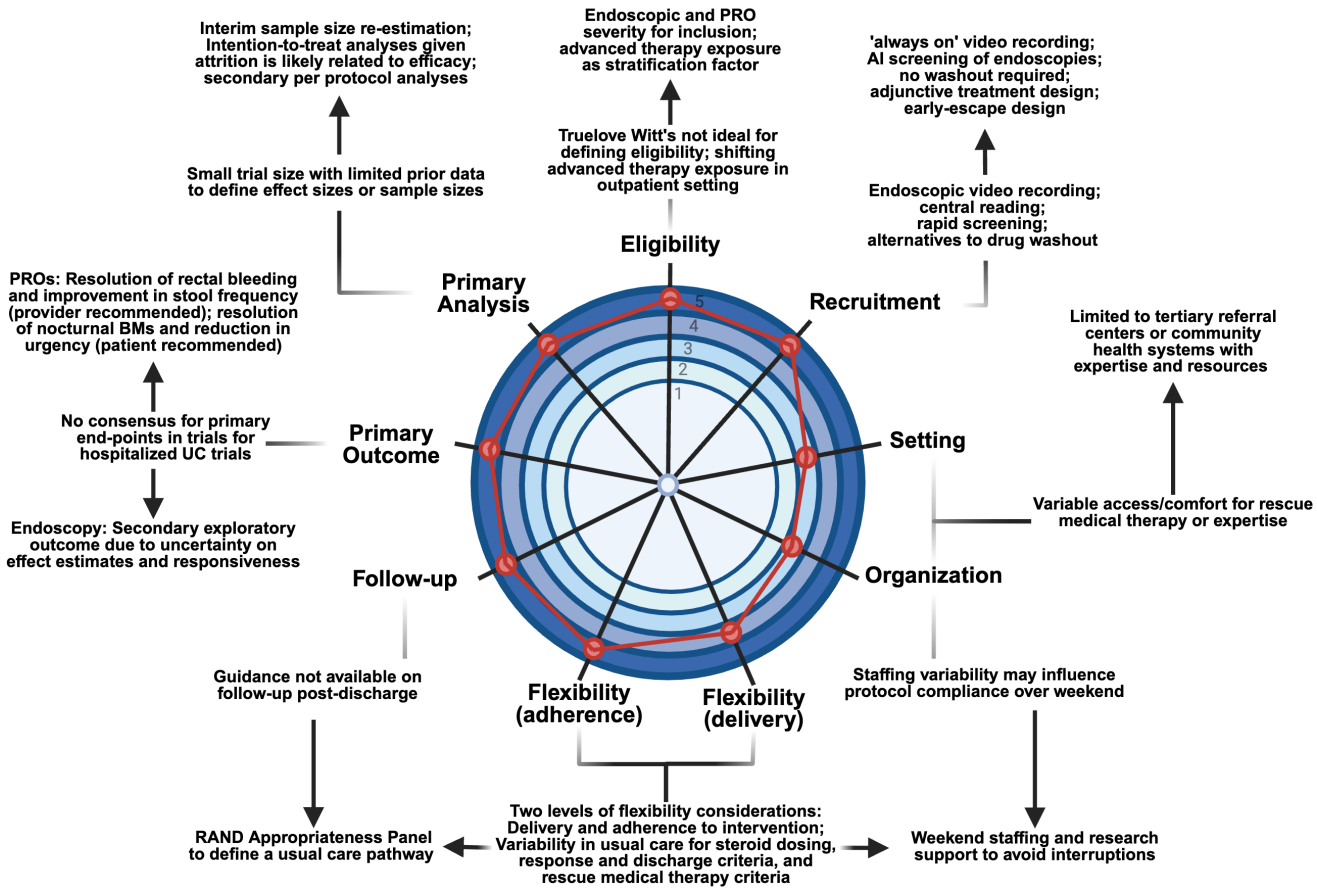

FIGURE 2 | PRECIS-2 domains, gaps identified in each domain for hospitalised ulcerative colitis trials, and decisions made to design a pragmatic trial for hyperbaric oxygen therapy. PRECIS-2 domains are outlined, barriers to each domain identified and decisions made or actions taken to overcome those barriers. A score of 5 (outer circle) represents a very pragmatic choice for this domain, a score of 1 (inner circle) represents a very explanatory choice for this domain and a score of 3 represents an equally pragmatic/explanatory choice for this domain. AI, artificial intelligence; BMs, bowel movements; IV, intravenous; PRO, patient-reported outcome.

these are broken up into endoscopy occurring: (1) shortly or (2) immediately prior to hospitalisation, (3) on admission prior to or (4) shortly after starting intravenous steroids and (5) after being deemed a non-responder to intravenous steroids prior to starting rescue therapy. It is impractical to consider traditional approaches to central video recording for these scenarios where coordinators bring recording devices to procedures that are pre-scheduled. Investigators will therefore need to consider the utilisation of 'always on' video recording devices at the participating centres for passive video recording such that if a patient is identified after an endoscopy has already occurred, the recorded endoscopic video would be acceptable for enrolment [39, 49]. The second recruitment barrier to overcome as it relates to baseline endoscopic assessment of disease activity is the potential need for central endoscopy scoring of disease activity. This often takes up to 5 days in outpatient trials [40], thus positioning a patient outside the window of eligibility for early intervention trials requiring initiation within 24–48 h of admission or delaying use of rescue therapy by several days in steroid non-responders, which would be unethical for a patient at risk for immediate colectomy. Recent evidence demonstrates high levels of agreement between local and central readers for baseline endoscopy in outpatient trials [41], and the risk of local reader misclassification in this acutely ill population is possibly even lower than outpatient trials. Central reading prior to confirmation of enrolment and randomisation may therefore not be required, but this can be further de-risked by using artificial intelligence tools (i.e., AutoIBD [49]) for rapidly screening baseline endoscopy videos to confirm activity as the videos are transferred from enrolling sites to the central repository prior to randomisation. This helps provide an additional fail-safe mechanism for the clinical coordinating centre to interrupt recruitment and randomisation for insufficient endoscopic activity.

4.2 | Competing Risks for Corticosteroids and/or Rescue Therapy

Investigators should consider provider and patient acceptance or preferences of potentially delaying access to available medical rescue options, downstream impacts for offering alternative medical rescue options versus colectomy, and influence of prior exposures on efficacy of rescue therapies being studied. To optimise recruitment and avoid provider and patient concerns for delays in proven

TABLE 1 | PRECIS-2 domain decision gaps identified for clinical trials in hospitalised ulcerative colitis patients [15–18, 26–48].

Gap identified	Decision for trial or future trial considerations
Eligibility criteria	
Severity criteria: Indices (i.e., Truelove and Witts) used to define acute severe hospitalised UC flares were created in the pre-biologic era, may not capture relevant populations, and/or may not be most ideal for identifying patient populations of interest in whom outcomes during hospitalisation would represent clinically meaningful outcomes	Truelove Witt's criteria are not ideal for defining eligibility in hospitalised UC trials. Endoscopic severity coupled with more severe symptoms than outpatient trials provide balance between prognostic value and pragmatic considerations for trial enrolment feasibility and generalisability of study results to broader populations. Incorporation of labs (CRP, albumin) or prognostic indices should be considered after further validation
Advanced therapy exposure: Exposure to biologics, small molecules and/or steroid dependency in the outpatient setting are important prognostic factors, but they will enrich the hospitalised population for non-response to intravenous steroids and need for rescue therapy. Prior exposures will limit options for rescue therapy, possibly enriching the use of in-hospital colectomy	Increasing proportion of hospitalised UC patients with prior exposure to biologics/small molecules and/or steroid dependency on admission, increasing number of prior biologics/small molecules at hospitalisation. Impractical to exclude or limit these populations based on prior exposures and more appropriate to consider these factors for stratification to ensure balance across arms
Recruitment	
Disease activity assessment: Trials enrolling patients on admission or shortly after starting corticosteroids will need rapid assessment of endoscopic activity with central reading. Lower endoscopies are at times performed shortly prior to admission, limiting feasibility for repeat endoscopy, or they are done more acutely (evenings or weekends) in-hospital, limiting feasibility in consent prior to procedure	Local and central reader agreement exists for baseline assessments of endoscopic activity in UC trials, and active central reading may not be required for entry endoscopy. The availability of 'always on' video recording devices for endoscopy allows for passive collection of videos in outpatient and inpatient settings for confirmation and assessment of changes in disease activity as well as use of artificial intelligence for baseline screening
Competing risk for corticosteroids or rescue therapy: Provider and patient acceptance for being randomised to not have corticosteroids will vary by perceived benefit of intervention of interest and trial design. Provider and patient acceptance for delaying options available for current (colectomy, infliximab, cyclosporine) or emerging (JAK inhibitors) rescue therapy options to study interventions of interest will wane throughout the hospitalisation due to compounding risk of complications if use of rescue therapies is delayed and/or surgery is delayed. These factors may limit feasibility in recruitment and/or characteristics of recruited populations, impacting trial fidelity, interpretability and/or generalisability	Therapies not proven to be efficacious in outpatient settings should be studied as adjunctive strategies alongside intravenous corticosteroids. Therapies proven to be efficacious in the outpatient setting may be feasible for studying as a replacement to intravenous corticosteroids if an outpatient trial demonstrates rapid reductions in activity (within 5 days). Steroid-refractory patients should be identified as early as possible (day 3 non-responders) to allow providers to feel comfortable with the duration of exposure to intervention and still have alternative rescue therapies available. Early-escape designs may optimise feasibility in recruitment. Total time from start of corticosteroids to primary end-point assessment should be $\leq$14 days due to risk for post-operative complications if surgery is delayed
Setting and organisation	
Rescue medical or surgical therapy: Community hospitals may have limited expertise, experience/comfort, or support for administration of rescue medical therapy and performing more emergent colectomy. This is compounded by delays in referrals to academic centres with expertise due to access or bed availability. Trials aimed at preventing the need for in-hospital rescue therapy or trials aimed at improving outcomes (response rates, post-operative outcomes, re-admission) among hospitalised UC patients needing rescue therapy may be influenced by this variability in the community setting and the subsequent impact on outcomes	Although the ideal setting for pragmatic trials aimed at preventing the need for rescue therapy or optimising outcomes with rescue therapy is community hospitals where there is the greatest need and most identical organisation to usual care for ultimate implementation, hospitalised UC trials will need to be predominately conducted in tertiary referral centres with immediate in-house access to rescue therapies, surgeons and research resources for on-demand recruitment, to minimise impacts on trial fidelity and consistency in outcome measurements or influence on event rates. The ideal setting for trials aimed at testing novel rescue therapies is tertiary referral centres, given referral patterns in usual care

(Continues)

TABLE 1 | (Continued)

Gap identified	Decision for trial or future trial considerations
Flexibility in delivery and adherence	
Weekend staffing: The acuity of the patient population warrants daily monitoring and treatment, including over weekends, creating issues with staffing for research intervention delivery and assessments. Modifications to research intervention delivery or clinical assessments to skip weekends for convenience may risk trial fidelity. This is impactful across all settings and organisations	Weekend staffing support will be critical to identify for each site, with accompanying weekend trial operational support. Consideration should be given to rely on usual care assessments to optimise flexibility in delivery and adherence of intervention and trial protocol adherence
Usual care pathway in-hospital: Wide variability exists in routine care management of hospitalised UC patients, particularly for (1) corticosteroid dosing/type, (2) response criteria, (3) discharge criteria and (4) non-response criteria to define escalation to rescue medical therapy. Usual care pathway variability may influence trial outcomes, and it will vary by setting and organisation of trial implementation	RAND Appropriateness Panels for the setting and organisations where the intervention is being delivered will help ensure trail design decisions are in keeping with acceptable usual care pathways to optimise balanced flexibility in delivery and adherence without risking trial fidelity. The HBOT-UC Consortium addressed this for future trial considerations and provides a framework for other trial designs in this population
Follow-up	
Treat-to-target: Hospitalised UC patients represent the highest risk cohort for disease complications, but treat-to-target guidelines for follow-up assessments are primarily focused on outpatients. Guidance is not available on interval of follow-up and intensity of follow-up in the post-hospital setting	A follow-up clinic visit is recommended within 2–4 weeks of discharge to ensure stability and guide further treatment considerations, and this is an ideal window for the initial clinic visit. Endoscopy is recommended 3 months post-discharge to assess disease activity once steroid tapers have been completed and determine treatment modifications
Primary outcome	
Patient Reported Outcomes: Response and discharge criteria for hospitalised UC patients have not been formally defined, and current disease activity indices have not been rigorously validated in the hospitalised setting for use in clinical trials. Patient input into trial endpoints has not been considered for hospitalised UC trials	Resolution of rectal bleeding and improvements in stool frequency were determined to be the most valid endpoints to define response, and the Mayo score was felt to be the most validated assessment tool for these measures. Urgency and nocturnal bowel movements were recommended by patients to be incorporated as study endpoints
Global Assessments of Severity: Response criteria for biomarkers are not well defined in the literature and variability in baseline elevations in biomarkers influences changes. Uncertainty on use of physician global assessment for hospitalised UC patients	Biomarkers and physician global assessment should still be captured as secondary endpoints given the acuity of the population. These measures may provide a more global understanding of response to intervention
Endoscopy: No prior literature or data on responsiveness of current indices in-hospital and whether in-hospital endoscopy could serve as a secondary endpoint	Endoscopy was added as a secondary exploratory endpoint for HBOT-UC trial and will create data to use for future trial designs

Abbreviations: CRP, C-reactive protein; JAK, Janus Kinase; UC, ulcerative colitis.

rescue therapy, early-escape design components will need to be implemented where patients meeting certain criteria for disease worsening or lack of response could have early rescue therapy prior to the primary end-point assessment. Definitions for worsening or lack of response criteria will need to be clearly outlined to avoid variability in care delivery influencing trial fidelity, and the cohort selection will need to be carefully considered as it will substantially influence the likelihood of downstream rescue therapy selection or comfort. Trials considering Janus Kinase (JAK) inhibitors or other rapidly acting small molecules will need to be mindful of cohort selection (i.e., regulatory "warnings" in certain jurisdictions that JAK inhibitors should only be used for patients with inadequate responses to tumour necrosis factor (TNF) antagonists) and recognition that these specialised populations may be at higher risk for early use of surgical rescue therapy due to lack of availability or reduced efficacy for alternative medical rescue agents (i.e., inability to use or lower efficacy of infliximab after prior outpatient TNF-antagonist exposure, and lack of comfort or safety concern using cyclosporine after outpatient TNF-antagonist exposure in steroid only arm) [38]. Active comparator trials among patients observed to be corticosteroid non-responders who require rescue medical therapy will need to ensure the cohort would have an equal opportunity for use of either agent being studied and equal impact of prior exposures on efficacy (i.e., cannot include primary non-responders to TNF-antagonist comparing JAK inhibitor to Infliximab rescue for corticosteroid non-responders).

5 | Setting and Organisation: Where Is the Trial Being Done and What Expertise or Resources Are Needed to Deliver the Intervention?

The setting and organisation needed to conduct UC clinical trials are available at either tertiary referral academic centres or community-based gastroenterology practices with inpatient facilities possessing appropriate research infrastructure. The populations in these locations are very different in the outpatient setting, and for hospitalised UC patients there are unique features within these settings and organisations that may either benefit or hinder the conduct of trials in this population. The most notable influences on trial design for this population are access, comfort and expertise/experience with rescue medical and/or surgical approaches (Table 1; [15–17]).

5.1 | Rescue Medical or Surgical Therapy

Wide variability exists in practice patterns and care delivery for hospitalised UC patients [42]. Community hospitals may have limited resources, access, or expertise with in-hospital rescue medical or surgical therapy. They may then rely on referral to academic centres with expertise, but bed availability and access issues regarding timing of transfers may exert a downstream impact on outcomes of importance. This is most evident considering postoperative mortality rates for emergent colectomies for UC flares. The overall postoperative mortality in the US for UC patients who were discharged after undergoing a total abdominal colectomy is approximately 2%. Operations performed at low-volume hospitals were 2.5 times more likely to result in mortality. When the operation is done emergently in the hospital and/or the operation is delayed beyond 14 days after admission, there is a 3–5 times higher probability for post-operative mortality [15–17]. Community hospitals often have late (5–7 days after admission) referrals once patients have clearly demonstrated they will not respond to intravenous corticosteroids and require rescue therapy. This delay in transfer truncates the amount of time available to attempt rescue therapy without extending beyond the 14-day window when post-operative mortality increases. The potential hurdles pertaining to access and outcomes with rescue medical or surgical therapies may substantially influence the explanatory impact of the trial, and these trials will likely need to rely on sites with tertiary referral capabilities and limited inclusion of community health systems with resources for in-hospital rescue therapy and colorectal surgery, recognising that if the intervention works in these patients, then it could readily be extrapolated to community hospitals.

6 | Flexibility in Delivery and Adherence: How Should the Intervention Be Delivered and What Measures Are in Place to Make Sure That Participants Adhere to the Intervention?

The PRECIS-2 framework provides recommendations for considering flexibility as it relates to the intervention of interest; however, during our planning period, we recognised that variability in usual care may further influence trial results. We needed to therefore consider domains related to flexibility within 2 contextual factors: (1) flexibility in delivery and adherence to interventions over the weekend and (2) flexibility regarding delivery and adherence to standard of care (medical and surgical management of hospitalised UC patients) (Table 1).

6.1 | Weekend Staffing

Flexibility in adherence to the treatment interventions through the weekend may prove challenging depending on the intervention type due to weekend staffing variability across sites, particularly for infusion-based therapies that require specialised nursing or investigational pharmacy. To overcome this, trials will need to provide operational and financial support for weekend personnel, a practical consideration for all hospitalised UC trials where daily monitoring, treatment interventions and end-point assessments may fall on weekends, and where it is impractical to skip assessments or intervention delivery based on convenience or to keep patients hospitalised through a weekend to await further research-related care or assessments.

6.2 | Usual Care Variability

Wide variability is known to exist for hospitalised UC patients in adherence to preventive measures (venous thromboprophylaxis) and lab-based testing (*Clostridioides difficile*); however, these can easily be addressed through protocolised requirements in keeping with societal recommendations and best practices. Wide variability also exists in steroid dosing, response criteria, discharge criteria and non-response criteria to define escalation to rescue medical therapy. Furthermore, an emerging practice of early rescue infliximab to shorten hospital stays was identified. These latter factors carry substantial risk of influencing trial outcomes.

To address this, the consortium conducted a RAND Appropriateness Panel to answer key questions from participating sites regarding acceptable evidence-based standard of care recommendations [43]. Future investigators considering trials for hospitalised UC patients should consider use of these RAND Panel recommendations for comparability or approach trial design with a similar methodology to ensure stakeholder engagement and acceptance of decisions for usual care pathway factors that potentially influence primary outcome event rates (i.e., steroid dosing, response criteria for discharge or escalation to rescue therapy). This will help ensure that after enrolment and randomisation all sites will be comfortable delivering and adhering to the usual care pathways outlined in the trial protocol.

7 | Follow-Up: How Different Is the Intensity of Measurement and Follow-Up of Participants in the Trial and the Likely Follow-Up in Usual Care?

In-hospital follow-up daily for UC patients is considered standard of care, and all trials will have limited barriers to implementing this level of intensity for disease activity assessments. The primary consideration for intensity of follow-up

is in the post-discharge setting, where variability exists in follow-up practice patterns and clear recommendations on timing of follow-up are yet to be established. However, post-discharge follow-up is also critical given the known risk of disease relapse, re-hospitalisation and/or colectomy, which can persist for over a year after the index hospitalisation. The RAND Appropriateness Panel for the HBOT-UC Consortium defined post-discharge recommendations for follow-up and recommended a clinic visit within 2–4 weeks of discharge and a follow-up endoscopy within 3 months of discharge. Recommendations could not be made for longer term follow-up intervals due to heterogeneity in outpatient care pathways, but future work is needed to define optimal treat-to-target frameworks in the outpatient setting post-discharge and incorporation of this into hospitalised UC trial designs. Recent evidence has demonstrated that adaptative steroid-dosing designs impact efficacy assessments, and consideration should be given for fixed steroid dosing post-discharge as well as exploring various definitions for steroid-free remission in the post-discharge setting [50]. For future trials considering post-hospitalisation modification of disease risk with alternative in-hospital rescue therapies, the greatest risk for re-hospitalisation is within 30 and 90 days. It may therefore be reasonable to have a minimum follow-up clinic visit within 4 and 12 weeks of discharge for these secondary outcomes, but longer term (12-month) outcomes should also be captured to better define the natural history of disease and impacts of interventions.

8 | Primary Outcome: To What Extent Is the Trial's Primary Outcome Relevant to Participants?

The Mayo score is a validated instrument to measure disease activity and is routinely used for registration trials. Per FDA guidance for outpatient UC clinical trial endpoints, it is recommended that efficacy be assessed with the rectal bleeding and stool frequency sub-scores of the Mayo score in combination with the endoscopic sub-score of the Mayo score. The FDA specifically recommends against the use of the physician global assessment sub-score of the Mayo score since it is not a PRO and could introduce investigator conscious or subconscious bias and influence trial procedures. The recommended definition for clinical remission was (1) a rectal bleeding score of 0, (2) a stool frequency sub-score of 0 or 1 with at least a 1-point reduction in the stool frequency sub-score and (3) an endoscopy sub-score of 0 or 1. More recent industry-sponsored clinical trials for UC have evolved to a clinical remission definition of (1) a rectal bleeding score of 0, (2) a reduction in stool frequency sub-score of at least 1-point and (3) an endoscopy sub-score of 0 or 1 under FDA guidance [44].

No formal consensus exists regarding primary endpoints in clinical trials for UC patients hospitalised for flares. All prior consensus statements and regulatory guidance in UC have been for outpatient trials in UC, and UC patients who are hospitalised or have recently been hospitalised for flares have traditionally been excluded from these outpatient UC clinical trials. Societal guidelines do not specifically outline response criteria or definitions for response to medical therapy for hospitalised UC patients [28, 29]. The Toronto consensus statement and Oxford criteria outline criteria for non-response to steroids and need to transition to rescue medical therapy; however, they do not outline specific criteria for remission or criteria for discharging UC patients from the hospital [45, 46]. A recent systematic review of prior clinical trials for hospitalised UC patients identified a lack of consistency for endpoints [51]. Trials studying the efficacy of antibiotics, infliximab, or cyclosporine have used "improvement in stool frequency" and "resolution of rectal bleeding" as measures of response and remission [28, 29], and evidence-based reviews have suggested that "improvements" in stool frequency and resolution of rectal bleeding should serve as primary treatment targets for determining hospital discharges [18, 47]. This is further supported by a recent analysis of an acute severe UC trial for tofacitinib, where resolution of rectal bleeding as defined by the Mayo score was the most prognostic for post-discharge steroid-free clinical remission and endoscopic improvement [52]. This is also now in keeping with evolving patient-reported outcome definitions and core outcome sets for UC in outpatient trials [53]. Therefore, resolution of rectal bleeding (Mayo rectal bleeding sub-score of 0) and improvement in stool frequency (at least a 1-point reduction in Mayo stool frequency sub-score) may serve as optimal patient-reported endpoints for clinical response in these trials.

To ensure this primary outcome was relevant to potential participants, the consortium created a patient-centred care committee composed of UC patients. The primary outcome was reviewed with the committee, which agreed with the relevance and clinical importance. During the committee meeting, urgency and nocturnal bowel movements were identified as important to participants and incorporated as secondary endpoints. UC patients commented on the impact these symptoms have and the importance of resolving these symptoms prior to discharge from the hospital. These endpoints have also more recently been incorporated in the SPIRIT consensus as measures of disease modification [48], and they have increasingly been incorporated into outpatient trials. Future work will be needed to develop novel composite disease activity indices specific to this acutely ill population, and/or to study the relative responsiveness of currently available indices such as the Mayo score, Urgency Numeric Rating Scale, or Simple Clinical Colitis Activity Index sub-scores as endpoints.

9 | Primary Analysis: To What Extent Are All Data Included in the Analysis of the Primary Outcome?

Hospitalised UC trials will often fall within the designation of a small clinical trial due to sample size, and approaches to the primary analysis become critical. Our trial and others in this space should use an intention-to-treat analysis. In a trial of this complexity, with varying levels of potential influence on intervention delivery and usual care and the compounding background risk of using rescue medical or surgical therapy throughout the hospitalisation, it becomes attractive to consider using a per-protocol analysis to ensure comparisons are made between trial participants in each arm who strictly adhere to the planned treatment. This has multiple pitfalls, particularly for small clinical trials due to violation of the principle of randomisation, reduction in sample size

from excluding nonconforming participants, and the reason for the protocol violation or deviation may be a result of the intervention (adverse event) or worsening disease activity due to lack of efficacy (higher rate of early rescue therapy in one arm) [54]. Accordingly, it is imperative to follow an intention-to-treat principle for primary statistical analyses. The short

TABLE 2 | Gaps needing to be addressed for hospitalised UC trial designs.

Gap domain	Short term goal	Long term goal
How should we define populations meeting eligibility criteria for hospitalised UC trials?	Delphi consensus for admission/eligibility criteria with consideration for endoscopy, labs (CRP, albumin), symptom severity and prior advanced therapy exposures	Development and/or validation of a composite index or criteria that is prognostic of short (5–7 day) and long (30-day)-term outcomes, applicable across broad populations and jurisdictions, and accepted by regulatory bodies
How should patient preferences be incorporated into trial designs and/or randomisation/allocation to interventions?	Inclusion of patient-centred committees with patient advocates when designing trials to ensure acceptability of design and endpoints	Discrete choice experiments and development of trial methodology to actively incorporate patient preferences into randomisation or allocation to interventions/rescue
How should corticosteroids be dosed, and do prior treatment failures and/or exposures in the outpatient setting influence responses to different doses?	Comparison of objective steroid response rates when considering prior failure of advanced medical therapies and/or steroid dependency in the outpatient setting	Randomised controlled trials comparing corticosteroid dosing strategies to determine non-inferiority and allow for variability in dosing to optimise recruitment feasibility
How should endoscopy be incorporated into screening and end-point assessments for hospitalised UC trials?	Determine the need for central reading in hospitalised UC trials to define eligibility for enrolment; Determine short-term (5–7 day) responsiveness of current indices for use as secondary endpoints	Regulatory body interactions on use of alternative endoscopic indices (UCEIS) for approval if demonstrated to be more responsive and/or discriminative than currently accepted indices (Mayo endoscopy sub-score)
How should non-response to corticosteroids be defined to ensure consistency in use of rescue therapy?	Re-evaluation of non-response criteria for early (within the first 3 days) rescue therapy to align with shifting practice patterns for up-front use of rescue therapy, particularly in patients with prior advanced medical therapy exposure	Development and/or validation of a composite index or criteria that is prognostic of longer-term (90-day or 1-year) outcomes, consistent with practice patterns across broader jurisdictions, and accepted by regulatory bodies
How should response to corticosteroids or rescue therapy be defined to determine discharge criteria?	Determine the prognostic value of different levels of response and different clinical indices for post-discharge outcomes (re-hospitalisation, colectomy) of interest; Determine how indices should be used for re-randomisation of responder design post-discharge	Treat-to-target trials that incorporate hospitalised or recently hospitalised patients to determine if different thresholds or follow-up intensity are needed for treatment targets to reduce disease-related risks of complications
What should the primary outcome be for hospitalised UC clinical trials?	Assessment of endpoints for construct validity, particularly discriminative validity, responsiveness and face validity, particularly with regard to alignment with discharge criteria	Engagement with regulatory bodies to determine primary outcome for trials that would lead to regulatory approval for the indication of hospitalised UC flares
What should key secondary outcomes be for post-discharge for UC clinical trials?	Post-discharge follow-up within 30 and 90 days to define impacts of interventions on short-term risk for interval disease worsening, re-hospitalisation and colectomy	Define outpatient care pathways post-discharge and incorporate longer term (12–24 month) follow-up for hospitalised UC trials to study efficacy in modifying the natural history of disease

timeframe of the intervention, with patients often being immediately available in-hospital for the duration of the study, makes it less likely that hospitalised UC trials will have attrition for primary analyses. It is anticipated that missing data for secondary outcomes may occur for various reasons in trials (i.e., no endoscopy in patients undergoing colectomy or those responding early who are discharged and unable to schedule outpatient endoscopy within the allowed time window), and, as such, analysis considerations should be dependent on the mechanism of missing data. A composite endpoint approach can be considered to handle missing data due to early colectomy, whereby participants receiving a colectomy prior to the outcome assessment timepoint will be considered as having no success. Missing data due to lost follow-up may be handled using multivariate imputation with fully conditional specification under missing at random and missing not at random assumptions. Results should be compared across approaches to assess the effect of missing data, robustness to various model specifications and validity of specified models.

Given the potential for provider/patient variation in the usual care experience, and the possibility of unintentional interruption in intervention delivery (i.e., weekend staffing barriers, nursing delays in administration of rescue medical therapy, bed shortages), a secondary per protocol analysis should still be considered to allow for better interpretation of the effect of the intervention in hospitalised UC trials. This will often need to be limited to participants (1) who complete a minimum number of intervention doses/treatments, (2) without early (on or before day 3) colectomy as these patients may represent a more acutely ill population not clearly identified at enrolment who were less likely to tolerate a full intervention period and (3) those without unacceptable early treatment adjustments where providers may choose to use rescue therapy (i.e., infliximab) despite patients having a partial response to the intervention in an effort to get patients out of the hospital.

10 | Power Considerations: How Should Sample Size Be Estimated in the Absence of Strong Preliminary Data and Re-Estimated Over the Course of the Trial?

Currently, there are no placebo-controlled trial data for hospitalised UC patients to guide sample size estimates, and variations in cohorts across studies will make it difficult to rely on historic trials for accurate sample size estimations. Use of historic trials may still be feasible using Bayesian or alternative approaches [55]; however, care should be taken to ensure the historic populations are representative of the study population for key factors that may influence trial outcomes, such as disease severity and prior treatment exposures. Adequate powering of trials will likely prove to be one of the most challenging aspects in this population as newer therapies are considered. Recognising the degree of uncertainty in assumptions around outcome frequencies and postulated effect sizes in this population and the anticipated small size of trials in this population, which rules out the possibility of many sample size re-estimation approaches, investigators may consider performing an interim analysis for re-estimation of the sample size at approximately 50% information using a conditional power approach as described by Mehta and Pocock [56]. Prior to the interim analysis, the enrolment rate and loss to follow-up to date should be evaluated to determine a maximum feasible sample size (n_{maximum}). This feasible sample size will be determined prior to any review of the interim data. The thresholds for the promising conditional power (CP) zone will then be estimated incorporating n_{maximum} and following Mehta and Pocock. This approach relies on an interim analysis and the achievable maximum to construct 'favourable', 'promising' and 'unfavourable' conditional zones. The 'favourable' and 'unfavourable' zones support continuation with the planned sample size, with 'favourable' indicating sufficient power to determine the success of the intervention based on accrued data and 'unfavourable' indicating an unlikely benefit from increased sample size. The 'promising' zone suggests that interim analyses suggest a potential benefit of the treatment arm and that a sample size increase would substantially add to the power to detect this benefit. Importantly, this approach to sample size estimation does not inflate the type I error. Outpatient trials often utilise stopping criteria for futility; however, hospitalised UC trials will be much smaller, and even a few events occurring in either arm could dramatically shift estimates. Consideration should therefore be given to finishing studies even if interim sample size estimates suggest an unfavourable zone.

11 | Future Directions and Conclusion

We have outlined the pragmatic framework decisions used when designing clinical trials in hospitalised UC patients suffering from moderate–severe flares and how we have applied this framework to designing a trial for hyperbaric oxygen therapy (Figure 2), but gaps remain that need to be addressed when planning for future clinical trials in this population (Table 2). We anticipate this methodological framework could serve as a launch pad for large multi-national collaborative studies aimed at addressing these gaps, but regulatory interaction will be needed to ensure future work in this population yields evidence that would support approval of therapies for this orphan population.

Author Contributions

Parambir S. Dulai: conceptualization, methodology, supervision, funding acquisition, project administration, writing – original draft, writing – review and editing, investigation, visualization, resources. **Lauren Balmert Bonner:** methodology, formal analysis, supervision, funding acquisition, writing – original draft, writing – review and editing, investigation. **Charlotte Sadler:** methodology, writing – review and editing, supervision, investigation. **Laura E. Raffals:** writing – review and editing, investigation, methodology. **Gursimran Kochhar:** investigation, writing – review and editing. **Peter Lindholm:** investigation, writing – review and editing, supervision, methodology. **Jay C. Buckey Jr:** methodology, investigation, writing – review and editing, supervision. **Gary N. Toups:** investigation, writing – review and editing. **Libeth Rosas:** project administration, writing – review and editing. **Neeraj Narula:** methodology, writing – review and editing. **Vipul Jairath:** methodology, writing – review and editing. **Sailish Honap:** methodology, writing – review and editing. **Laurent Peyrin-Biroulet:** methodology, writing – review and editing. **Bruce E. Sands:** methodology, writing – review and editing. **Stephen B. Hanauer:** methodology, writing – review and editing, investigation. **Denise M. Scholtens:** methodology, formal analysis, investigation, writing – review and editing, funding acquisition, supervision. **Corey A. Siegel:** writing – review and editing, investigation, methodology.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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